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10/031,695	01/23/2002	Bernhard Hauer	51241	8284

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,695	HAUER ET AL.	
	Examiner	Art Unit	
	YONG D. PAK	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14,16-18 and 20* is/are pending in the application.

4a) Of the above claim(s) *1-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 14, 16-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/EP00/07252.

The amendment filed on May 19, 2008, amending claims 12 and 20, has been entered.

Claims 1-12, 14, 16-18 and 20 are pending. Claims 1-11 are withdrawn. Claims 12, 14, 16-18 and 20 are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on May 19, 2008, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In view of the amendment of claim 12, the rejection of claims 12 and claims 14 and 16-18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention has been **withdrawn**.

In view of the amendment of claim 20, the rejection of claim 20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been **withdrawn**.

Claims 12 and 20 and claims 14 and 16-18 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 20 recite the phrase “monooxygenase having the amino acid sequence of SEQ ID NO:2 and containing one functional mutation” and “monooxygenase having the amino acid sequence of SEQ ID NO:2, wherein SEQ ID NO:2 contains one functional mutation". The metes and bounds of this phrase in the context of the claims are not clear to the Examiner. It is not clear to the Examiner how a polypeptide can have the amino acid sequence of a given sequence identifier (SEQ ID NO:2 in the instant case) and also have mutations. A polypeptide either has the amino acid sequence of given sequence identifier or it does not. As applicants have not provided a definition for the above phrase, Examiner has interpreted the claims broadly to encompasses a method of using a monooxygenase which is a variant of SEQ ID

NO:2, wherein said variant comprises one functional mutation in each of amino acid sequence positions 87 and 188 of SEQ ID NO:2 and optimally at least one additional function mutation in the one of the amino acid sequence positions 26, 47, 72, 74 and 354 of SEQ ID NO:2. Examiner has given the same interpretation while considering the claims for all other rejections.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 14, 16-18 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12, 14, 16-18 and 20 are drawn to a method for the enzymatic production of subterminally hydroxylated aliphatic carboxylic acids with a cytochrome P450 monooxygenase having the amino acid sequence according to SEQ ID NO:2, wherein said monooxygenase of contains a functional mutation at position 87 and 188 and optionally at least one additional functional mutation at positions 26, 47, 72, 74 and 354.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the limitation of “containing” or “contains” mutations at positions 87 and 188 and optionally at positions 26, 47, 72 and 354 provide no description on the structure of other parts of the mutant

monooxygenase because (1) the claimed variant is not limited to only those mutations at positions 87, 188 and 26, 47, 72 and 354, and (2) the transitional term "containing" or "contains" is inclusive or open-ended and does not exclude additional, unrecited elements, such as mutations at other positions. Therefore, while the mutant monooxygenase comprises the recited mutations/substitutions, the same mutant comprises any amino acids in any other positions. Therefore, Examiner has interpreted the claims broadly to encompass a method of using a polynucleotide encoding any or all mutants of SEQ ID NO:2, wherein said mutant comprises of one or more amino acid mutation/substitution at amino acid positions corresponding to 87 and 188 and optionally at positions 26, 47, 72 and 354 of SEQ ID NO:2 and one or more amino acid mutation/substitutions at any other amino acid positions. Therefore, the claims encompass a method for the production of subterminally hydroxylated aliphatic carboxylic acids using a polynucleotide encoding mutant monooxygenase having any structure, except at the recited amino acids.

The specification only teaches a method for hydroxylating 15-para-nitrophenoxycarboxylic acids (pNCA), 12-pNCA, 10-pNCA or 8-pNCA with a polynucleotide encoding a mutant of a cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the mutant consists of mutations at position 26, 47, 74, 87, 188 and/or 354 of SEQ ID NO:2. These limited examples are not enough and does not constitute a representative number of species to describe the whole genus and there is no evidence on the record of the relationship between the structure of a modified cytochrome P450 monooxygenase of SEQ ID NO:2 consisting of substitutions at residues 26, 47, 74, 87,

188 and/or 354 of SEQ ID NO:2 and the structure of any recombinants, variants and mutants of SEQ ID NO:2 or any cytochrome P450 monooxygenase derived from SEQ ID NO:2. Therefore, the specification fails to describe a representative species of the genus comprising variants and mutants of SEQ ID NO:2 or any recombinants, variants and mutants of any cytochrome P450 monooxygenase, derived from SEQ ID NO:2 or from any source, used to produce subterminally hydroxylated aliphatic carboxylic acids.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 12, 14, 16-18 and 20.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the claims have been amended to describe mutants of SEQ ID NO:2, obtained by performing specific mutations at two specific positions and optional further specific mutations. Examiner respectfully disagrees. The limitation of "containing" or "contains" functional mutations at positions 87 and 188 and optionally at positions 26, 47, 72 and 354 provide no description on the structure of other parts of the mutant monooxygenase because (1) the claimed variant is not limited to only those mutations at positions 87, 188 and 26, 47, 72 and 354, and (2) the transitional term

"containing" or "contains" is inclusive or open-ended and does not exclude additional, unrecited elements, such as mutations at other positions. Therefore, while the mutant monooxygenase comprises the recited mutations/substitutions, the same mutant comprises any amino acids in any other positions. The genus comprising any or all recombinants, variants and mutants of any monooxygenase does not possess any common attributes other than having monooxygenase activity. Therefore, the specification lacks description of a representative number of species to describe the whole genus. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which

embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genus used in the method includes species which are widely variant in structure. As such, the disclosure solely functional features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus.

Hence the rejection is maintained.

Claims 12, 14, 16-18 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enzymatic production of specific subterminally hydroxylated aliphatic carboxylic acids by using a polynucleotide encoding a mutant of a cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the mutant consists of a substitution at positions 87 and 188 and optionally at positions 26, 47, 72, 74 and 354 and using 15-para-nitrophenoxycarboxylic acids (pNCA), 12-pNCA, 10-pNCA or 8-pNCA as substrates, does not reasonably provide enablement for a method for the production of any subterminally hydroxylated aliphatic carboxylic acids using a polynucleotide encoding a mutant of SEQ ID NO:2 or any cytochrome P450 monooxygenase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. (See rejection of "derived" under 35 U.S.C. 112, 2nd paragraph).

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir.

1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 12, 14, 16-18 and 20 are drawn to a method for the enzymatic production of subterminally hydroxylated aliphatic carboxylic acids with a monooxygenase having the amino acid sequence according to SEQ ID NO:2, wherein said monooxygenase of contains a functional mutation at position 87 and 188 and optionally at least one additional functional mutation at positions 26, 47, 72, 74 and 354.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the limitation of “containing” or “contains” mutations at positions 87 and 188 and optionally at positions 26, 47, 72 and 354 provide no description on the structure of other parts of the mutant monooxygenase because (1) the claimed variant is not limited to only those mutations at positions 87, 188 and 26, 47, 72 and 354, and (2) the transitional term "containing” or “contains” is inclusive or open-ended and does not exclude additional, unrecited elements, such as mutations at other positions. Therefore, while the mutant monooxygenase comprises the recited mutations/substitutions, the same mutant comprises any amino acids in any other positions. Therefore, Examiner has interpreted the claims broadly to encompass a method of using a polynucleotide encoding any or all mutants of SEQ ID NO:2, wherein said mutant comprises of one or

more amino acid mutation/substitution at amino acid positions corresponding to 87 and 188 and optionally at positions 26, 47, 72 and 354 of SEQ ID NO:2 and one or more amino acid mutation/substitutions at any other amino acid positions. Therefore, the claims encompass a method for the production of subterminally hydroxylated aliphatic carboxylic acids using a polynucleotide encoding mutant monooxygenase having any structure, except at the recited amino acid positions.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of P450 monooxygenase variants and mutants, broadly encompassed by the claims. The claims encompass compounds with widely varying structure and properties. However, in this case the disclosure is limited to a method for hydroxylating 15-para-nitrophenoxycarboxylic acids (pNCA), 12-pNCA, 10-pNCA or 8-pNCA with a polynucleotide encoding a mutant cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the mutant consists of mutations at residue 26, 47, 74, 87, 188 or 354 of SEQ ID NO:2.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method for hydroxylating 15-para-nitrophenoxycarboxylic acids (pNCA), 12-pNCA, 10-pNCA or 8-pNCA with a

polynucleotide encoding a mutant cytochrome P450 monooxygenase of SEQ ID NO:2, wherein the mutant consists of mutations at residue 26, 47, 74, 87, 188 or 354 of SEQ ID NO:2. It would require undue experimentation of the skilled artisan to make the claimed variants and mutants of SEQ ID NO:2 or any P450 monooxygenases and use the claimed variants and mutants of any P450 monooxygenase to produce any subterminally hydroxylated aliphatic carboxylic acids. In view of the great breadth of the claim, amount of experimentation required to make and use the polynucleotides in the claimed method, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by the claimed method.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method for the enzymatic production of subterminally hydroxylating

aliphatic carboxylic acids using any or all mutants and variants of SEQ ID NO:2, because the specification does not establish: (A) regions of the substrate binding region of SEQ ID NO:2 which may be modified without affecting P450 monooxygenase activity or having an altered substrate profile (except at the recited amino acid positions); (B) the general tolerance of P450 monooxygenase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function except at the recited amino acid positions); (D) aliphatic carboxylic acids which are subterminally hydroxylated with any P450 monooxygenases; (E) a rational and predictable scheme for selecting aliphatic carboxylic acids with an expectation of obtaining a subterminally hydroxylated aliphatic carboxylic acids by incubating said substrates with any P450 monooxygenase; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for the production of subterminally hydroxylated aliphatic carboxylic acids using any or all variants and mutants of SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any or all mutants and variants of SEQ ID NO:2 having the desired biological characteristics recited in the claim is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly,

extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the claims have been amended to describe mutants of SEQ ID NO:2, obtained by performing specific mutations at two specific positions and optional further specific mutations. Examiner respectfully disagrees.

comprising SEQ ID NO:2" encompasses polypeptides which are recombinants, variants or mutants of any monooxygenase used in a method of producing any hydroxylated aliphatic carboxylic acids. As discussed above, the limitation of "containing" or "contains" functional mutations at positions 87 and 188 and optionally at positions 26, 47, 72 and 354 provide no description on the structure of other parts of the mutant monooxygenase because (1) the claimed variant is not limited to only those mutations at positions 87, 188 and 26, 47, 72 and 354, and (2) the transitional term "containing" or "contains" is inclusive or open-ended and does not exclude additional, unrecited elements, such as mutations at other positions. Therefore, while the mutant monooxygenase comprises the recited mutations/substitutions, the same mutant comprises any amino acids in any other positions.The only "structure" recited by the claims is that the mutant monooxygenase has (1) a Val, Ala or Leu at position 87 and Asn, Gln, ARg, Lys, Ala, Gly, Ser or Trp at position 188 or (2) Val, Ala or Leu at position 87 and Asn, Gln, ARg, Lys, Ala, Gly, Ser or Trp at position 188 and two contiguous amino acids of SEQ ID NO:2. Two to Four amino acids out of almost 1000 amino acids

(SEQ ID NO:2 has 1048 amino acids) amounts to 0.2 to 0.4% of the whole structure of a given monooxygenase and therefore, Examiner has construed the claims as having no structure. Therefore, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation. While the art may teach in general the structure of P450 monooxygenase, conserved amino acid sequences, and etc, such teachings will not reduce the burden of undue experimentation on those of ordinary skill in the art.

Hence the rejection is maintained.

Conclusion

Claims 12, 14, 16-18 and 20 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652